Sex-specific Differences in Response to First-line *Helicobacter pylori* Eradication Therapy with Vonoprazan, Amoxicillin, and Clarithromycin

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ABSTRACT

Background: *Although gender medicine has been promoted in medical research and patient care, limited information is available on sex-specific differences in response to first-line Helicobacter pylori eradication therapy. Therefore, this retrospective study investigated sex-specific differences in response to first-line H. pylori eradication therapy with vonoprazan, amoxicillin, and clarithromycin.*

Method: *The study included 314 patients who received vonoprazan-based triple therapy (20 mg vonoprazan, 750 mg amoxicillin, and 200 or 400 mg clarithromycin; twice daily for 7 days) as first-line H. pylori eradication therapy at Fuyoukai Murakami Hospital from March 1, 2015, to April 30, 2019. First-line eradication rates were determined by intention-to-treat (ITT) and per protocol (PP) analyses. Sex-specific differences in the rate of drug-related treatment-emergent adverse events (TEAEs) were also monitored. Fisher's exact test was used for identifying sex-specific differences.*

Results: *First-line eradication rates were >95% in ITT and PP analyses regardless of sex, without significant sex-specific differences [ITT analyses: males 95.3% (203/213) vs. females 96.0% (97/101), p = 1.0; PP analyses: males 95.3% (203/213) vs. females 96.0% (95/99), p = 1.0]. However, the rate of drug-related TEAEs was significantly higher in females than in males [males 4.2% (9/213) vs. females 17.8% (18/101), p < 0.001]. In particular, skin rash occurred only in females [males 0% (0/213) vs. females 10.9% (11/101), p < 0.00001].*

Conclusion: *Females experienced more drug-related TEAEs than males during first-line H. pylori eradication therapy with vonoprazan-based triple therapy. In particular, skin rash was observed only in females.*

Keywords: *Helicobacter pylori, eradication, treatment-emergent adverse event, sex-specific difference*

ABSTRAK

Latar belakang: *Meskipun kedokteran berdasarkan jenis kelamin telah dipromosikan dalam penelitian medis dan pelayanan pasien, ketersediaan informasi mengenai perbedaan respon terapi eradikasi Helicobacter pylori lini pertama berdasarkan jenis kelamin masih terbatas. Oleh karena itu, studi retrospektif ini menginvestigasi perbedaan respon terapi eradikasi Helicobacter pylori lini pertama dengan vonoprazan, amoxicillin, dan clarithromycin berdasarkan jenis kelamin.*

Metode: *Studi ini mengikutsertakan 314 pasien yang mendapat terapi tripel vonoprazan (20 mg vonoprazan, 750 mg amoxicillin, dan 200 atau 400 mg clarithromycin; dua kali sehari selama 7 hari) sebagai terapi eradikasi H. pylori lini pertama di Rumah Sakit Fuyoukai Murakami dari 1 Maret 2015 hingga 30 April 2019. Angka eradikasi lini pertama ditentukan dengan analisis intention-to-treat (ITT) dan per protocol (PP). Perbedaan berdasarkan jenis kelamin dalam angka efek samping yang muncul akibat pengobatan juga dimonitor. Uji Fisher's exact digunakan untuk menilai perbedaan berdasarkan jenis kelamin.*

Hasil: *Angka eradikasi lini pertama adalah > 95% pada analisa ITT dan PP, terlepas dari jenis kelamin, tanpa perbedaan berdasarkan jenis kelamin yang bermakna [analisis ITT: laki-laki 95,3% (203/213) vs. perempuan 96,0% (97/101), p = 1,0; analisis PP: laki-laki 95,3% (203/213) vs. perempuan 96,0% (95/99), p = 1,0]. Namun, angka efek samping akibat pengobatan secara signifikan lebih tinggi pada perempuan dibandingkan pada laki-laki [laki-laki 4,2% (9/213) vs. perempuan 17,8% (18/101), p < 0,001]. Secara spesifik, ruam kulit hanya dialami oleh perempuan [laki-laki 0% (0/213) vs. perempuan 10,9% (11/101), p < 0,00001].*

Simpulan: *Lebih banyak jumlah perempuan yang mengalami efek samping akibat pengobatan dibandingkan laki-laki dalam terapi eradikasi Helicobacter pylori lini pertama dengan terapi tripel berbasis vonoprazan. Secara spesifik, ruam kulit ditemukan hanya pada perempuan.*

Kata kunci: *Helicobacter pylori, eradikasi, efek samping akibat pengobatan, perbedaan berdasarkan jenis kelamin*

INTRODUCTION

Helicobacter pylori infection is associated with peptic ulcers and gastric cancer. The International Agency for Research on Cancer recommends population screening for *H. pylori* and its eradication to reduce the incidence of gastric cancer.[1] In Japan, the number of patients receiving *H. pylori* eradication therapy is increasing markedly since its use was first approved for the treatment of chronic gastritis by the Japanese health insurance in 2013. The efficacy of antibiotics against *H. pylori* is enhanced by the coadministration of antisecretory drugs.[2] Vonoprazan is a novel oral potassium-competitive acid blocker that has a greater acid-inhibitory effect than proton pump inhibitors (PPIs) such as esomeprazole and rabeprazole.[3] Furthermore, the Japanese health insurance approved vonoprazan for *H. pylori* eradication in 2015. Many studies have reported first-line *H. pylori* eradication therapy with vonoprazan, amoxicillin, and clarithromycin (vonoprazan-based triple therapy) to have higher efficacy than PPI-based triple therapy.[4]

Sex-specific differences in the therapeutic effects of drugs and occurrence of adverse drug reactions are recognized; furthermore, pharmacokinetic and pharmacodynamic changes can affect desired and adverse effects.[5] Although gender medicine has been promoted in medical research and patient care, limited information is available on sex-specific differences in response to first-line *H. pylori* eradication therapy. Therefore, this study investigated sex-specific differences in response to first-line vonoprazan-based triple therapy for *H. pylori* eradication.

METHOD

This retrospective study included a total of 314 patients who received first-line vonoprazan-based triple therapy (20 mg vonoprazan, 750 mg amoxicillin, and 200 or 400 mg clarithromycin; twice daily for 7 days) as first-line *H. pylori* eradication therapy from March 1, 2015, to April 30, 2019, at Fuyoukai Murakami Hospital. *H. pylori* infection was diagnosed using the rapid urease test (PyloriTek®; Eidia, Tokyo, Japan). None of the patients had a history of drug allergy. Esophagogastroduodenoscopy confirmed the absence of malignancy. *H. pylori* eradication was evaluated 8 weeks after the eradication therapy completion using the ^{13}C-urea breath test (UBit-100®; Otsuka Pharmaceutical, Tokyo, Japan), with a cut-off value of 2.5‰. The Institutional Ethics Committee approved the study, and all participants provided oral informed consent.

The following characteristics were analyzed between sexes: age (≥ 65 years), gastric mucosal atrophy (moderate or severe), nodular gastritis, history of peptic ulcers, and rate of study dropout. Gastric mucosal atrophy was diagnosed according to the Kimura–Takemoto classification as mild (C-1 or C-2), moderate (C-3 or O-1), or severe (O-2 or O-3).[6] First-line eradication rates were calculated using intention-to-treat (ITT) and per protocol (PP) analyses, and the rates of drug-related treatment-emergent adverse events (TEAEs) were recorded. Fisher's exact test was used to identify significant sex-specific differences. Statistical analysis was performed with EZR (easy R, version 1.37), and p values of < 0.05 were considered statistically significant.[7]

RESULTS

The characteristics of the patients included in the study are summarized in Table 1. Approximately two-third of patients (67.8%, 213/314) were males, and the median age of patients was 51.5 years (range, 17–78 years). Most patients (84.1%, 264/314) had mild gastric

mucosal atrophy. There were no significant sex-specific differences in terms of all characteristics (Table 2).

Table 1. Characteristics of the study patients (n = 314)

Age (years)	51.5 (43, 59)*
Males	213 (67.8%)
Gastric mucosal atrophy	
Mild	264 (84.1%)
Moderate	30 (9.6%)
Severe	20 (6.4%)
Nodular gastritis	13 (4.1%)
Past history of peptic ulcers	56 (17.8%)
Dropouts	2 (0.6%)

*: median (25%, 75%)

Table 2. Characteristics of males and females

	Males (n = 213) n (%)	Females (n = 101) n (%)	p*
Age			
≥ 65 years	20 (9.4)	12 (11.9)	0.550
Gastric mucosal atrophy			
Moderate or severe	34 (16.0)	16 (15.8)	1
Nodular gastritis	6 (2.8)	7 (6.9)	0.126
Past history of peptic ulcers	43 (20.2)	13 (12.9)	0.155
Dropouts	0	2 (2.0)	0.103

*: Fisher's exact test

First-line eradication rates were >95% in ITT and PP analyses regardless of sex. The differences in first-line eradication rates between males [95.3% (203/213) and 95.3% (203/213), respectively] and females [96.0% (97/101) and 96.0% (95/99), respectively] in ITT (p = 1.0) and PP analyses (p = 1.0) were not significant (Table 3). The rate of drug-related TEAEs was significantly higher in females (17.8%, 18/101) than in males (4.2%, 9/213; p < 0.001). Skin rash only occurred in females (10.9%, 11/101; p < 0.00001; Table 3).

DISCUSSION

First-line eradication rates observed in the present study were 2.7–3.4% higher than those (92.6%; 300/324) reported in a Japanese multicenter, prospective study.[8] First-line vonoprazan-based triple therapy is recommended as a highly effective regimen regardless of sex because it exceeds the goal of > 90% eradication established as a global consensus for *H. pylori* treatment in the era of increasing antibiotic resistance.[9] Drug-related TEAEs were observed in 8.6% of patients (27/314), and the dropout rate was 0.6% (2/314), consistent with the values reported in a systematic review and meta-analysis on the efficacy of vonoprazan-based triple therapy for *H. pylori* eradication, which reported a pooled TEAE of 8.1% and pooled dropout rate due to TEAEs of 0.5%.[10] Two patients who discontinued treatment because of rash or epigastralgia with acute mid-grade fever 2 days after the initiation of treatment achieved bacterial eradication. Extremely early eradication of *H. pylori* possibly leads to an inflammatory reaction caused by the death of *H. pylori*, which is known as Jarisch–Herxheimer reaction.

The present study revealed sex-specific differences in terms of the development of skin rash. Males and females differ in their pharmacological responses; thus, females have a higher incidence of allergic skin rash.[5] In addition, 63.6% of patients (7/11) presented skin rash after first-line *H. pylori* eradication therapy completion (Table 4). Ito et al reported a specific anti-*H.*

Table 3. First-line eradication rate and drug-related treatment-emergent adverse events (TEAEs) in males and females

	Males (n = 213)	Females (n = 101)	p
First-line eradication rate			
Intention-to-treat analysis	95.3% (203/213)	96.0% (97/101)	1
Per protocol analysis	95.3% (203/213)	96.0% (95/99†)	1
Drug-related TEAEs	9 (4.2%)	18 (17.8%)	0.0001
Diarrhea	3 (1.4%)	0	0.554
Dysgeusia	0	2 (2.0%)	0.103
Skin rash	0	11 (10.9%)	0.000003
Pruritus	1 (0.5%)	0	1
Dyspepsia	5 (2.3%)	3 (3.0%)	0.715
Constipation	0	1 (1.0%)	0.322
Oral candidiasis	0	1 (1.0%)	0.322

*: Fisher's exact test

†: Two patients withdrew because of rash or epigastralgia with acute mid-grade fever

Table 4. Characteristics of patients with skin rash

	Age (years)	Sex	Interval from start of treatment to onset (days)	Clarithromycin dosage	Eradication
Patient 1	60	Female	2	200 mg twice daily	Success
Patient 2	54	Female	3	200 mg twice daily	Success
Patient 3	60	Female	3	200 mg twice daily	Success
Patient 4	36	Female	7	200 mg twice daily	Success
Patient 5	41	Female	8	200 mg twice daily	Success
Patient 6	71	Female	8	200 mg twice daily	Success
Patient 7	29	Female	9	200 mg twice daily	Success
Patient 8	40	Female	9	200 mg twice daily	Success
Patient 9	55	Female	9	200 mg twice daily	Success
Patient 10	50	Female	10	200 mg twice daily	Success
Patient 11	60	Female	10	200 mg twice daily	Success

pylori immune reaction in patients with skin rash after *H. pylori* eradication therapy completion, suggesting that skin rash is not necessarily a drug-related TEAE.[11] Sex-specific differences in immune responses may also result in differential susceptibility of males and females to skin reactions as well as autoimmune diseases. It is often difficult to identify the cause of skin rash, particularly in patients using antibiotics.[11] However, it is important to distinguish other causes of adverse drug reactions because the appropriate use of antibiotics is limited if physicians overestimate antibiotic-associated adverse drug reactions.

The present study has several limitations. This study was designed as a single-center retrospective study. Therefore, large-scale surveys are necessary in the future. Further, drug-induced lymphocyte stimulation test was not performed. Further investigation of the cause of skin rash is needed.

CONCLUSION

The rate of drug-related TEAEs was significantly higher in females than in males during first-line *H. pylori* eradication with vonoprazan-based triple therapy, particularly skin rash.

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